

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **75-318**

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 75-318

APPLICANT: Invamed, Inc.

DRUG PRODUCT:

Ticlopidine Hydrochloride Tablets, 250 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,



Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-318 SPONSOR: Invamed, Inc.

DRUG & DOSAGE FORM: Ticlopidine HCl Tablets

STRENGTH(S): 250 mg

TYPE OF STUDY: Single dose fasting and non-fasting studies

STUDY SITE:

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic and dissolution data of ticlopidine tablets. The firm has conducted single-dose fasting and nonfasting studies, and dissolution testing on test and reference products. The results of the studies indicate that Invamed's 250 mg tablets are bioequivalent to the reference product, Roche Laboratories' Ticlid® 250 mg tablets. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{inf}$, and LC_{max} are in the acceptable range of 80-125 for single-dose study. As required, under fed conditions, the test/reference ratios for PK parameters were within 0.8-1.2.

DISSOLUTION:

The test product 250 mg tablets meet the agency's dissolution specifications (non-USP Method). The amount of drug dissolved from the test product was NLT in 45 minutes.

PRIMARY REVIEWER: S.P. Shrivastava, Ph.D. **BRANCH:** II

INITIAL /S/ DATE 4/30/98

BRANCH CHIEF: S. G. Nerurkar, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE 5/1/98

DIRECTOR

DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL /S/ DATE 5/4/98

DIRECTOR

OFFICE OF GENERIC DRUGS: Douglas L. Sporn

INITIAL: _____ DATE _____

BIOEQUIVALENCY COMMENTS

ANDA: 75-318

APPLICANT: Invamed, Inc.

DRUG PRODUCT:

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The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

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Printed in final on 4/27/98

Endorsements: (Final with Dates)

HFD-650/ SShrivastava

HFD-655/ SNerurkar

HFD-617/ L. Sanchez or N. Chamberlin

HFD-650/ D. Conner

ISI 4/30/98

5/1/98

ISI 5/4/98

BIOEQUIVALENCY - UNACCEPTABLE

JAN 21, 1998

1. **FASTING STUDY (STF)**

Clinical:

Analytical

Strengths: 250 mg

Outcome: AC

2. **FOOD STUDY (STP)**

Clinical:

Analytical

Strengths: 250 mg

Outcome: AC

3. **DISSOLUTION DATA (DIS)**

250 mg

Outcome: AC

no
An

Outcome Decisions:

AC - Acceptable

WINBIO COMMENTS:

Ticlopidine Hydrochloride, 250 MG Tablets
ANDA #75-318
Reviewer: S.P. Shrivastava
WP #75318SD.198

Invamed, Inc.
Dayton, NJ
Submitted:
January 21, 1998

**REVIEW OF TWO BIOEQUIVALENCE STUDIES,
AND ONE SET OF DISSOLUTION TESTING DATA**

I. OBJECTIVES

Review of Invamed's two *in vivo* bioequivalence studies comparing its 250 mg strength ticlopidine hydrochloride tablets to Syntex (Roche's) 250 mg strength Ticlid[®] tablets, under fasting and non-fasting conditions. The firm has also submitted dissolution testing results in water.

II. BACKGROUND

Drug Substance: Ticlopidine is a platelet aggregation inhibitor which is indicated to reduce the risk of thrombotic stroke in patients who have had a thrombotic stroke or have experienced stroke precursors. The drug inhibits the fibrinogen binding of platelets to form blood clots. The exact mechanism of action, however, is unknown.

After oral administration of a single 250 mg dose, ticlopidine is rapidly absorbed, with peak plasma levels (C_{max}) reached in about 2 hours. Absorption is greater than 80%, and administration after meals results in a 20% increase in the extent of absorption (AUC). Ticlopidine HCL displays non-linear pharmacokinetics and the clearance decreases markedly on repeated dosing. The drug's elimination half-life ($T_{1/2}$) following single oral doses of 250 mg to healthy males has been reported as about 7-8 hours. The drug binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. This binding is non-saturable over a wide concentration range.

Ticlopidine is rapidly metabolized by the liver; only trace amounts of intact drug are found in the urine. Over twenty metabolites have been identified in the urine and plasma. The drug is inactive *in vitro*, so a metabolite of ticlopidine may be the active antithrombotic agent; however, the product labeling states that no such metabolite has been isolated. Clearance of ticlopidine decreases with age and steady-state trough values in elderly patients (mean age 70 years) were about twice those in young volunteers.

The drug is marketed as Ticlid[®] 250 mg tablets (Syntex). The recommended dosage is 250 mg twice a day given with food to increase gastric tolerance.

III. SUMMARY OF BIOEQUIVALENCE STUDY PROTOCOLS

A. Single-Dose Fasting Study

1. Protocol # 962265

This open label, randomized, single-dose, two-way crossover study was conducted with 44 (4 alternate) healthy male volunteers in accordance with the protocol. Forty-four subjects, # 1-42, 44 and 46 were used in the study. Subject # 43 dropped out in Period-2 due to personal reasons. In each period, subjects received a single 250 mg dose of either Invamed's ticlopidine hydrochloride tablets or Syntex's Ticlid[®] tablets following an overnight fast. There was a two-week wash-out period between treatments. Blood samples were collected pre-dose and for 72 hours after each dose. Plasma concentration of ticlopidine was measured by a fully validated procedure. Pharmacokinetic and statistical analyses were performed to compare the test and reference products.

2. Objective of the study

The objective of this study was to determine the bioequivalence of two ticlopidine hydrochloride formulations after administration of single doses to healthy volunteers under fasting conditions.

3. Study design: Randomized, single-dose, two-way crossover study.

4. Study sites Clinical study:
 Analytical study:

5. Study dates: 8/2/97 - 8/20/97

Clinical study: 8/3/97 -8/20/97
Analytical study: 8/27/97 - 10/6/97
Storage Time: 64 Days

6. Investigators: Principal Investigators

D.

A. Test: 250 mg Ticlopidine hydrochloride tablets (Invamed, Lot #D970509);
 Lot Size Potency - 99.2%.

B. Reference: 250 mg Ticlid[®] Tablets (Roche Labs., Lot #07633A);
 Exp. Date 1/99; Potency - 102.0%.

Randomization Scheme: See Attachment-1.

7. Dosing: All doses were administered with of water. Subjects fasted overnight pre- and 4 hours post-dosing.

8. Subjects: The 44 (plus 4 alternate) subjects entered, and 43 completed the study. Subjects

were normal healthy male volunteers between the ages 18-43 years, and within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects.

9. Food and fluid intake: Standard meals were served at 4 and 9 hours post-dose, and at appropriate times as scheduled on each day. The drug products were administered with mL of water. Water was allowed *ad lib.* except during one-hour pre- and one-hour, post-dosing periods.
10. Washout period: Two weeks between dose administration.
11. Blood samples: In each period, 10 mL of blood samples were collected in tubes containing EDTA at 0.0, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours. Plasma was separated and all plasma samples were stored frozen at -22°C until ready for analysis.
12. Adverse reactions: On each dosing period subjects were asked to report any signs or symptoms judged to be drug related.
13. Pharmacokinetic and statistical analysis: Statistical analyses were performed on the pharmacokinetic parameters for ticlopidine hydrochloride. 90% confidence intervals were calculated for $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max} .

B. Limited-Food Study

1. Protocol # (protocol #962266)
2. Study design: Randomized, single-dose, three-way crossover, six sequence study under fasting/non-fasting conditions.
3. Study Sites and Investigators: Same as in the fasting study
4. Study dates: Clinical study: 10/25/97 - 11/25/97
Analytical study: 11/28/97 - 12/18/97
Total Storage Period: 54 Days
5. Treatments:
 - A. Test: 1 x 250 mg Ticlopidine hydrochloride Tablets (Invamed, Lot #D970509, under fasting conditions.
 - B. Test: 1 x 250 mg Invamed ticlopidine hydrochloride tablets (Invamed, Lot #D970509, under non-fasting conditions.

C. Reference: 1 X 250 mg Ticlid[®] tablet (Roche), Lot #07633A, Exp. Date 1/99) under non-fasting conditions.

Randomization Scheme: See Attachment-2.

6. Dosing: All doses were administered with 240 mL of water at room temperature following an overnight fast or within 30 minutes of starting the breakfast depending on the dosing schedule.
7. Subjects: Twenty-four subjects entered and 22 completed the study. Subject #21 withdrew due to personal reasons, and Subject #20 was withdrawn due to medical reasons.
8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of water. Water was allowed *ad lib.* except during one-hour pre-dose and one-hour post-dose periods.
9. Wash-out period: Two weeks between dosage administration.
10. Blood samples: Ten mL blood samples were collected at 0.0, 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours.

IV. PRE-STUDY VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

Methods: Ticlopidine hydrochloride in the plasma samples was analyzed by _____ equipped with _____

- a. Specificity: No interfering peaks were detected for ticlopidine hydrochloride or internal standard in the blanks, standards or pre-dose samples.
- b. Sensitivity: _____ /mL
- c. Linearity: 2-1049.01 ng/mL. Average correlation coefficients were (r^2) 0.99 or better.
- d. Precision:

Inter-Day: Results are shown in Table 1.

Table 1. Calibration Standards for Ticlopidine Hydrochloride

Theoretical Conc, ng/mL	2.0	4.0	35.0	99.9	349.7	499.5	599.4	699.3	839.2	1049.0
Sample Number (n)	4	4	4	4	4	4	4	4	4	4
Mean Conc.	2.07	3.99	34.0	94.2	349.5	514.2	634.4	710.9	842.8	994.7
Precision, % CV	4.8	11.3	6.3	4.2	4.1	3.8	8.3	3.7	2.7	4.9
Accuracy, % Diff	+3.6	-0.1	-2.6	-5.7	0.0	+2.9	+5.8	+1.7	+0.4	-5.2

e. Intra-Day Precision: Ticlopidine hydrochloride sample data are summarized in Table 2.

Table 2. Intra-Day Precision of Ticlopidine Hydrochloride Samples

Theoretical Conc, ng/mL	5.01	300.51	798.15
n	10	10	10
Mean	5.529	296.32	793.745
Precision, %	6.0	3.9	3.5
Accuracy, % Diff.	+10.4	-1.4	-0.6

f. Recovery: Percent extracted vs. unextracted data for the analyte and internal standard are given in Tables 3 and 4.

Table 3. Ticlopidine Hydrochloride Recovery Data (n=6)

Nominal Conc., ng/mL	5.00	300.24	540.44
Recovery, %	79.0	81.5	82.2
%CV	6.0	5.1	9.1

Table 4. Recovery of Internal Standard (Imipramine; n=6)

Nominal Conc., (μg/mL)	QC A 2.51	QC B 5.01	QC C 7.52	Average
Recovery, %	58.7	63.2	63.5	61.8
%CV	8.5	11.0	6.8	8.8

- g. Stability of Ticlopidine hydrochloride : Stability was checked under various conditions, including refrigeration at 4 °C, in biological matrix at bench-top for 6.5 hours, during four freeze-thaw cycles, on auto-sampler for 17.5 hours, and long-term stability at -22 °C for 152 days. Plasma samples are stable under the study conditions.

Storage Test	Conc. ng/mL	Storage Period	Temperature	% Diff.
System-Check (Autosampler) (n=10)	5	17.5 Hours	4 °C	+1.2
	300.24			-10.3
	540.44			-10.0
Four Freeze-Thaw Cycles (n=8)	5	4 Cycles	Room/-22 °C	+2.0
	540.44			-4.3
Bench-Top (n=8)	5	6.5 Hours	22 °C	-2.5
	540.44			-1.1
Long-Term Stab. (n=10)	5.02	152 Days	-22 °C	+8.7
	541.86			+7.6

V. RESULTS

A. Single-Dose Fasting Study

Within-Study Validation

	Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=24 2.00	9.0	- 5.6
	n=24 3.99	6.8	0.6
	n=25 34.95	5.6	4.2
	n=25 99.86	4.8	4.2
	n=23 349.50	3.7	-1.1
	n=25 499.29	3.4	-4.9
	n=25 599.15	3.4	0.4
	n=25 699.01	4.3	-0.8
	n=24 838.81	2.8	1.9
	n=24 1048.51	3.4	1.1
QC Samples;	n=49 4.99	7.3	7.2
	n=48 299.57	2.9	1.1
	n=45 798.87	1.9	2.1

1. **Blood/Plasma Drug Concentration:** Based on pharmacokinetic anomalies, Subject #26 was considered as outlier. The mean plasma concentration data with (n=44) and without (n=43) Subject #26 are given in Tables 5, 8 and graphic profiles are shown in Attachments 3, 4.
2. **Pharmacokinetic Parameters:** Mean PK parameters and statistical analysis are given in Tables 6-7. Individual data are shown in Attachments 5a-6b. Subject #26 showed an extremely low C_{max} , and AUCs. Therefore, ANOVA analysis without Subject #26 (n=43) was also performed. PK data are given in Tables 9-10.
 - The 90% CI for LAUCs are within 80-125% as required (Tables 7, 10).
 - ANOVA analysis showed no significant treatment, period or sequence effects on $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} .
 - Individual Test/Reference ratios for AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and T_{half} averaged between 0.91-1.03.
 - The ratios of AUC_{0-t}/AUC_{0-inf} averaged 94 and 95%, respectively, for test and reference.
 - None of the subjects had C_{max} at first non-zero time point.
 - Plasma concentration-time profiles were checked for subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.
3. **Adverse Reaction:** No significant differences between test and reference products were observed (See the table below).

<u>Sign/Symptom</u>	<u>Test</u>	<u>No. Of Subjects</u>		<u>Drug Related</u>
		<u>Reference</u>		
Headache	1	0		Possible/Probable
Cramps	1	0		Possible/Probable
Dizziness	1	1		Possible/Probable
Stomachache	1	1		Possible/Probable
Loose stools	1	2		Possible/Probable
Fatigue	1	0		Possible/Probable
Nausea	1	0		Possible/Probable

Conclusion: The *in vivo* fasting study is acceptable.

TABLE 5. MEAN PLASMA TICLOPIDINE HYDROCHLORIDE LEVELS FOR TEST AND REFERENCE PRODUCTS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS;(n=44))

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	35.89	54.18	30.00	70.30	1.20
1	247.13	222.81	199.49	171.89	1.24
1.33	349.37	261.82	306.20	221.13	1.14
1.67	416.08	277.72	354.99	239.93	1.17
2	389.40	246.75	381.90	267.61	1.02
2.33	327.82	225.35	348.98	266.31	0.94
2.67	253.70	179.82	305.70	245.88	0.83
3	194.72	145.28	240.77	216.42	0.81
3.5	134.38	102.51	166.22	148.91	0.81
4	100.67	75.43	117.41	100.94	0.86
6	41.27	29.43	45.42	37.90	0.91
8	31.44	21.84	31.67	22.89	0.99
12	15.10	9.95	15.82	12.84	0.95
16	10.31	6.84	11.27	8.10	0.91
24	6.83	4.72	7.57	5.28	0.90
36	4.90	4.32	5.00	5.04	0.98
48	2.08	2.18	2.26	2.32	0.92
72	0.93	1.55	1.14	1.90	0.82

1=TEST, 2=REFERENCE

TABLE 6. TEST MEAN/REFERENCE MEAN RATIOS (n=44; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1532.63	920.44	1639.21	1054.93	0.93
AUCT	1434.77	931.77	1481.02	1018.56	0.97
CMAX	490.39	289.79	488.27	285.98	1.00
KE	0.05	0.03	0.05	0.03	1.04
LAUCI	1231.11	0.72	1304.78	0.72	0.94
LAUCT	1099.77	0.81	1090.21	0.94	1.01
LCMAX	396.12	0.72	393.78	0.76	1.01
THALF	16.26	6.89	15.79	5.57	1.03
TMAX	1.74	0.48	1.91	0.54	0.91

1=TEST, 2=REFERENCE

TABLE 7. LSMEANS AND 90% CONFIDENCE INTERVALS (n=44)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1529.14	1598.99	0.96	88.25	103.01
AUCT	1434.77	1481.02	0.97	89.28	104.48
CMAX	490.39	488.27	1.00	92.25	108.62
LAUCI	1233.20	1263.73	0.98	90.45	105.28
LAUCT	1099.77	1090.21	1.01	90.06	113.00
LCMAX	396.12	393.78	1.01	90.12	112.29

1=TEST 2=REFERENCE

TABLE 8. MEAN PLASMA TICLOPIDINE HYDROCHLORIDE LEVELS FOR TEST AND REFERENCE PRODUCTS
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS; (n=43))

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	36.59	54.62	30.00	70.30	1.22
1	252.29	222.76	204.13	171.12	1.24
1.33	356.39	260.86	313.32	218.59	1.14
1.67	424.86	274.76	363.19	236.45	1.17
2	397.70	243.38	381.90	267.61	1.04
2.33	334.88	223.05	357.05	263.96	0.94
2.67	259.23	178.12	312.72	244.28	0.83
3	198.86	144.35	246.30	215.82	0.81
3.5	137.26	101.90	170.02	148.50	0.81
4	102.86	74.89	120.06	100.57	0.86
6	42.14	29.21	46.40	37.78	0.91
8	32.07	21.70	32.32	22.75	0.99
12	15.38	9.89	16.19	12.76	0.95
16	10.55	6.73	11.53	8.00	0.91
24	6.99	4.65	7.75	5.21	0.90
36	5.02	4.31	5.12	5.04	0.98
48	2.13	2.18	2.31	2.32	0.92
72	0.95	1.56	1.16	1.92	0.82

1=TEST, 2=REFERENCE

TABLE 9. TEST MEAN/REFERENCE MEAN RATIOS (n=43; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	1532.63	920.44	1639.21	1054.93	0.93
AUCT	1465.42	920.07	1514.98	1005.10	0.97
CMAX	500.54	285.21	499.19	279.94	1.00
KE	0.05	0.03	0.05	0.03	1.04
LAUCI	1231.11	0.72	1304.78	0.72	0.94
LAUCT	1158.68	0.74	1195.43	0.73	0.97
LCMAX	414.86	0.66	422.54	0.60	0.98
THALF	16.26	6.89	15.79	5.57	1.03
TMAX	1.75	0.48	1.91	0.54	0.92

1=TEST, 2=REFERENCE

TABLE 10. LSMEANS AND 90% CONFIDENCE INTERVALS (n=43)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	1529.14	1598.99	0.96	88.25	103.01
AUCT	1467.31	1514.96	0.97	89.24	104.46
CMAX	501.29	500.09	1.00	92.06	108.42
LAUCI	1233.20	1263.73	0.98	90.45	105.28
LAUCT	1160.59	1196.43	0.97	88.24	106.64
LCMAX	415.64	423.56	0.98	88.41	108.91